



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Attorney Docket No.: 30523/105/ANRO

In Patent Application of

Henryk LUBON et al.

Serial No.: 07/943,246

Filed: September 10, 1992

For: EXPRESSION OF ACTIVE HUMAN PROTEIN C IN MAMMARY TISSUE  
OF TRANSGENIC ANIMALS USING A LONG WAP PROMOTER

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APPLICATION DIVISION-403

**INFORMATION DISCLOSURE STATEMENT**  
**UNDER 37 CFR 1.56**

The Honorable Commissioner of  
Patents and Trademarks  
Washington, D.C. 20231

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Sir:

Submitted herewith on Form PTO-1449 is a listing of documents known to Applicants in order to comply with Applicants' duty of disclosure pursuant to 37 CFR 1.56. A copy of each listed document is being submitted to comply with the provisions of 37 CFR 1.97-1.99.

The submission of any document herewith, which is not a statutory bar, is not intended as an admission that such document constitutes prior art against the claims of the present application. Applicants do not waive any rights to take any action which would be appropriate to antedate or otherwise remove as a competent reference any document which is determined to be a prima facie prior art reference against the claims of the present application.

**The Commissioner is hereby authorized to  
charge any deficiency or credit any over-  
payment to Deposit Account No. 19-0741.**

CONCISE EXPLANATION OF  
RELEVANCE OF EACH DOCUMENT

- A1    Bang *et al.*, U. S. patent No. 4,775,624, dated Oct. 4, 1988, describes vectors and compounds for expression of human protein C.
- A2    Bang *et al.*, U. S. patent No. 4,992,373, dated Feb. 12, 1991, describes vectors and compounds for direct expression of activated human protein C.
- A3    Meade *et al.*, U.S. patent No. 4,873,316, dated Oct. 10, 1989, describes the isolation of exogenous recombinant proteins from the milk of transgenic mammals.
- A4    European Patent Application 0 264 166, dated April 20, 1988, describes transgenic animals secreting desired proteins into milk.
- A5    European Patent Application 0 279 582, dated Aug. 24, 1988, describes DNA sequences to target proteins to the mammary gland for efficient secretion.
- A6    PCT International Application WO 88/00239, dated Jan. 14, 1988, describes a method of producing a substance comprising a peptide, involving incorporating a DNA sequence coding for the peptide into a gene of a mammal (such as sheep) coding for a milk whey protein in such a way that the DNA sequence is expressed in the mammary gland of the adult female mammal.
- A7    PCT International Application WO 88/01648, dated Mar. 10, 1988, describes expression of heterologous proteins by transgenic lactating mammals.

- A8 PCT International Application WO 90/05188, dated May 17, 1990, describes a genetic construct of which protein-coding DNA comprises introns, which is designed for protein production in transgenic animals.
- A9 Denman et al. (September 1991), *Bio/Technology* 9: 839-843, describes the purification and characterization of a variant human tissue-type plasminogen activator produced by . transgenic expression in goat milk.
- A10 Ebert et al. (September 1991), *Bio/Technology* 9: 835-838, describes the generation of transgenic goats and the analysis of transgenic production of a variant of human tissue-type plasminogen activator in the goats' milk.
- A11 Gordon et al. (November 1987), *Bio/Technology* 5: 1183-1187, describes the production of human tissue plasminogen activator in transgenic mouse milk.
- A12 Krimpenfort et al. (September 1991), *Bio/Technology* 9: 844-847, describes the generation of transgenic dairy cattle using *in vitro* embryo production.
- A13 Walls et al. (1989), *Gene* 81: 139-149, describes the amplification and secretion of correctly processed recombinant human protein C using multicistronic plasmids in the human 293 cell line.
- A14 Wright et al. (September 1991), *Bio/Technology* 9: 830, describes the high level expression of active human alpha-1-antitrypsin in the milk of transgenic sheep.
- A15 Yan et al. (July 1990), *Bio/Technology*: 8 655-661, describes the characterization and novel purification of recombinant human protein C from three mammalian cell lines.

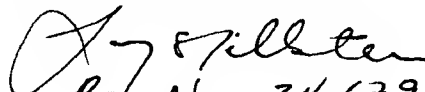
- B1 Velander et al. (1990), "The Expression of Human Protein C in the Milk of Transgenic Mice," 1990 Annual Meeting of the American Institute of Chemical Engineering, November 11-16, 1990, is an abstract relating to work some of the present inventors was included in a compilation of abstracts circulated to participants at the meeting.
- B2 Grinnell et al. (1990), "Native and Modified Recombinant Human Protein C and Related Anticoagulants", Chapter 3, Bruley and Drohan, Eds., Portfolio Co., The Woodlands, Texas, relates to the expression of protein C in transfected mammalian cells in culture.
- B3 Wydro, R.M. (1990), "Transgenic Production of Protein C" appeared in "Protein C and Related Anticoagulants, An International Symposium," a compilation of material relating to a symposium held February 26-27, 1992 in San Diego, CA , and reports on attempts to produce protein C in the milk of transgenic mice which did not result in the production of significant quantities of protein C.
- C1 Hogan et al. (1981), MANIPULATING THE MOUSE EMBRYO, Cold Spring Harbor Laboratory, New York, pgs. 155-203, relates to general methods for producing transgenic mice.
- C2 Grinnell et al. (1987), *Biotechnology* 5: 1189-1192, reports on trans-activated expression of fully gamma-carboxylated recombinant human protein C.
- C3 Pittius et al. (1988), *Proc. Natl. Acad. Sci., U.S.A.* 85: 5874-5878, reports that a milk protein gene promoter directs the expression of human tissue plasminogen activator cDNA to the mammary gland in transgenic mice"

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- C4 Colpan et al. (1984), *J. Chromatography* 296: 339-353, reports on HPLC purification of high-molecular-weight nucleic acids using nucleogen, a macroporous ion exchanger.
- C5 Clark et al. (Jan., 1987), *TIBTECH* 5: 20-24, reviews the production of pharmaceuticals from transgenic livestock.
- D1 Campbell et al. (1984), *Nucleic Acids Research* 12: 8686-8697, reports on the sequences of the rat and mouse whey acid protein genes.

Applicants respectfully request that the listed documents be considered by the Examiner and formally be made of record in the present application and that an initialled copy of Form PTO-1449 be returned in accordance with MPEP §609.

Respectfully submitted,

  
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December 31, 1992

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